Final Office Action on the Merits of a RCE

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Application

2. Claims 39-56 and 65-75 are pending in the present application. The instant claims stand rejected as indicated below.

Claim Rejections - 35 USC § 112

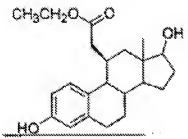
3. The rejection of claims 57-64 under 35 USC 112, first paragraph, as failing to comply with the written description requirement is made moot by the cancellation of the instant claims.

4. The rejection of claim 76 under 35 USC 112, second paragraph, as being indefinite is made moot by the cancellation of the instant claim.

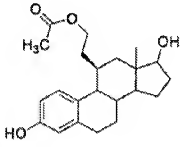
5. Claims 39-56 and 65-75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application

was filed, had possession of the claimed invention. The claims as amended recites the proviso wherein:

said compound is other than compound E11-2,2Rev of Table 1 and Figure 8 having the chemical structure:



However, the specification setforth the structure of E11-2,2Rev as:



E11-2,2Rev

. This is a new matter rejection.

Claim Rejections - 35 USC § 103

6. The rejection of claims 57-64 and 76 under 35 USC 103(a) over van den Broek et al. (US 3,972,906) is made moot by the cancellation of the instant claims.

7. The rejection of claims 57-64 and 76 under 35 USC 103(a) over van den Broek et al. (US 3,972,906) in view of Cameron et al. (US 2001/0025051), Palkowitz

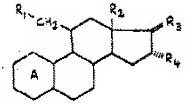
(US 6,268,361) and Bodor et al. (US 4,617,298) is made moot by the cancellation of the instant claims.

8. The rejection of claims 39-56 and 65-75 under 35 USC 103(a) over (a) van van den Broek et al. (US 3,972,906) and (b) van den Broek et al. (US 3,972,906) in view of Cameron et al. (US 2001/0025051), Palkowitz (US 6,268,361) and Bodor et al. (US 4,617,298) is maintained.

Applicant argues (a) the present methods only become available as methods because of the discovery of the unexpected SERM activity, i.e., combination of estrogenic/antiestrogenic activity, of the compounds not taught by van den Broek et al., (b) estrogen receptor agonists are contraindicated for treatment of post-menopausal symptoms because of the enhanced risk of breast cancer, (c) the only estrogenic activity disclosed or suggested by van den Broek is for certain short-chained 11β-substituted steroidal compounds (in contradistinction to the present invention) not the longer chained groups (at least 5 non-hydrogen atoms in the chain), (d) van den Broek teaches away from the present method claims inasmuch as the biological activity taught by the reference is contraindicated in the claimed methods and the present compounds do not possess the estrogenic activity required by the reference, (e) there is no evidence of a lead compound in the reference because there is no biological data which can serve to provide an indication of a lead compound, (f) the teachings of Cameron, Palkowitz or Bodor related to the use of estrogen agonists which are combinable with the teachings of van den Broek simply emphasize the use of short-chain 11β-

compounds exhibiting agonist activity, (g) Cameron teaches the skilled artisan to avoid estrogen agonists and to use SERMS in breast cancer, Palkowitz teaches the of estrogen agonists in estrogen-sensitive cancer is contraindicated and Bodor makes an oblique reference to the use of estrogen compounds in the treatment of breast cancer but does not provide any disclosure relevant to the present invention. Applicant's arguments were considered but not persuasive for the following reasons.

First, van den Broek teaches 11-substitued steroid of the formula:

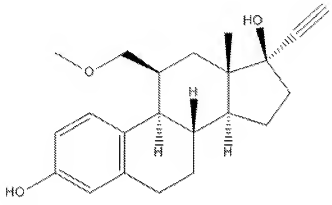


in which
R_1 = a free, esterified or etherified hydroxyl group or halogen;
R_2 = an alkyl group with 1–4 C-atoms;
R_3 = O or (αY) (βZ), in which Y = H or a saturated or unsaturated alkyl group with 1–4 C-atoms and Z = a free, esterified or etherified hydroxyl group;
R_4 = H or a free or esterified hydroxyl group; and ring A including carbon atom 6 is

in which
R_5 = H or a free, esterified or etherified hydroxyl group,

(see col. 1, lines 19-48) and

exemplifies



. However, as noted in the previous Office Action and above, the reference teaches both 11β-alkoxy and 11β-alkcarbonyloxymethyl derivatives for use in the treatment of estrogen-deficiency syndromes. The art teaches disorders such as osteoporosis and breast cancer are estrogen-deficiency syndromes. The art also teaches that said disorders are treatable with the use of estrogenic compounds.

Even if one agrees that the reference teaches short chain 11β-compounds, van den Broek teaches:

> By a lower alkoxy- or acyloxy group is meant an alkoxy- or acyloxy group with 1–8 C-atoms such as, for example, methoxy, ethoxy, cyclopentyloxy, cyclohexenyloxy, acetoxy, pivalyloxy, butyryloxy, oenanthyloxy or hemisuccinyloxy.

(see col. 2, lines 23-28) and, thus, the reference encompasses compounds wherein R as defined by the instant claims is a side chain of at 5 non-hydrogen atoms in length. The fact that the reference does not realize the compounds have a combination of estrogenic/antiestrogenic activity, does not nullify the teaching by van den Broek that the prior art compounds are useful in the treatment of estrogen-dependent syndromes such as osteoporosis as recited by instant claims 39 and 65 or breast cancer as recited by instant claim 48.

Second, applicant argues estrogen receptor agonists are contraindicated for treating post-menopausal symptoms. However, there are numerous teachings of the use of estrogens, including conjugated estrogens, i.e., Premarin, for treatment of menopausal symptoms (references will be provided upon request).

As the skilled artisan is well aware, most if not all pharmaceutical agents have some form of adverse effect(s) which vary from patient to patient. As evidenced by Cameron, Palkowitz and Bodor, estrogens are used in the treatment of menopausal symptoms such as osteoporosis and breast cancer:

> [0008] Estrogen is the agent of choice in preventing osteoporosis or post menopausal bone loss in women; it is the only treatment which unequivocally reduces fractures. However, estrogen stimulates the uterus and is associated with an increased risk of endometrial cancer. Although the risk of endometrial cancer is thought to be reduced by a concurrent use of a progestogen, there is still concern about possible increased risk of breast cancer with the use of estrogen.

(see Cameron, page 1);

> At this time, the only generally accepted method for treatment of post-menopausal osteoporosis is estrogen replacement therapy. Although therapy is generally successful, patient compliance with the therapy is low primarily because estrogen treatment frequently produces undesirable side effects.

(see Palkowitz, col. 2, lines 10-15) and

> At the present time, estrogens are generally administered to control symptoms of menopause; for postmenopausal osteoporosis, dysmenorrhea, menorrhagia, amenorrhea, atrophic vaginitis, ovarian dwarfism and post partum breast engorgement; in combination with progestins in oral contraceptives; in breast cancer; and in men in prostatic carcinoma.

(see Bodor, col. 3,lines 25-31).

However, applicant points to the teachings of adverse effect as a teaching away or

contraindication for treatment of post-menopausal symptoms utilizing estrogen receptor agonists. As recognized by applicant, tamoxifen is a non-steroidal SERM and the art as evidenced by Palkowitz teaches said compounds have side-effects which are not ideal:

> The third major pathology associated with post-menopausal syndrome is estrogen-dependent breast cancer and, to a lesser extent, estrogen-dependent cancers of other organs, particularly the uterus. Although such neoplasms are not solely limited to a post-menopausal women, they are more prevalent in the older, post-menopausal population. Current chemotherapy of these cancers has relied heavily on the use of anti-estrogen compounds such as, for example, tamoxifen. Although such mixed agonist-antagonists have beneficial effects in the treatment of these cancers, and the estrogenic side-effects are tolerable in acute life-threatening situations, they are not ideal. For example, these agents may have stimulatory effects on certain cancer cell populations in the uterus due to their estrogenic (agonist) properties and they may, therefore, be contraproductive in some cases.

(see col. 2, lines 40-57). Thus, as suggested by applicant for estrogenic agonists, SERMs are contradicated in the treatment of postmenopausal symdromes due to its effect on estrogen sensitve cancer such as uterine cancer.

The fact here is that the art teaches the use of estrogenic agonists for the treatment of menopausal symptoms and van den Broek teaches compounds encompassed by the instant claims for use in treating estrogen-dependent symptoms which is known in the art to be inclusive of menopausal symptoms such as osteoporosis and breast cancer.

Third, applicant argues there is no evidence of a lead compound because there is no biological data which can serve to provide an indication of a lead compound. Applicant is suggesting the term "lead compound" is defined by the Court in the same

way as a researcher in the pharmaceutical field, i.e., a compound having undergone preclinical and/or clinical trials or being the most active for a given activity. However, said term includes any compound that an examiner would use as the basis for a structural obviousness argument. In the examiner's opinion there remains no legal basis that a prior art compound selected to show obviousness based on close structural similarity and/or an equivalency teaching must be particularly singled out for its activity. The fact that it is taught to possess activity is sufficient and where there is no extrinsic evidence to doubt its activity, should not be disqualified where the compound(s) has been otherwise shown to be an obvious variant of applicants' invention.

In summary, the cited prior art makes obvious the use of the claimed compound for treatment of menopausal symptoms such as osteoporosis and breast cancer. The fact that the prior art teaches adverse effects with the use of estrogens does not nullify the treatment methods taught therein. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco, Inc.* 190 F.3d 1342, 1347, 51 USPQ 2d 1943, 1947 (Fed. Cir.) 1999). Thus, while known compositions may be claimed in new methods of treating conditions for which they were previously unknown to have therapeutic value, the claiming of a new *property* which was inherently present in the prior art composition at all times does not distinguish it over the prior art. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430,433 (CCPA 1977). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only

that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.* 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); *In re Woodruff*, 919 F.2d 1575, 1578, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990) ("It is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable.") See also MPEP §2112.

For these reasons and those given in the previous Office Actions, the rejection of claims 39-56 and 65-75 under 35 USC 103(a) over (a) van den Broek et al. (US 3,972,906) and (b) van den Broek et al. (US 3,972,906) in view of Cameron et al. (US 2001/0025051), Palkowitz (US 6,268,361) and Bodor et al. (US 4,617,298) is maintained.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Telephone Inquiry

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BARBARA P. BADIO whose telephone number is (571)272-0609. The examiner can normally be reached on M-F from 6:30am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 571-272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BARBARA P. BADIO/
Primary Examiner, Art Unit 1628